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HFD-19 FOI

Amlodipine Besylate
Tablets 2.5, 5, 10 mg
NDA 19-787
Reviewer: Ameeta Parekh, Ph.D.
PC
L2-S, 1-D, 5-O
[redacted]

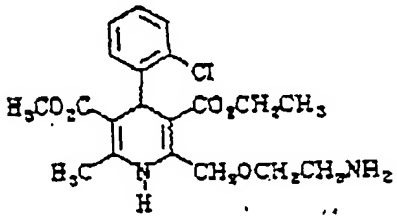
Pfizer Inc.,
Eastern Point Road
Groton, CT 06340
Submission Date:
December 22, 1987
August 2, 1988
February 22, 1990

OCT 10 1990

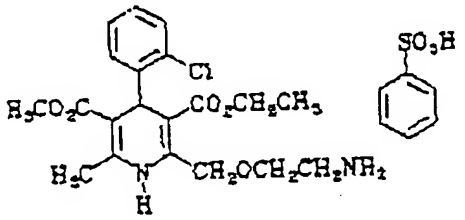
Review of an Original NDA

Background:

Amlodipine is a dihydropyridine antihypertensive and anti-anginal agent belonging to the class of calcium channel blockers. Amlodipine besylate is 3-ethyl-5-methyl-2-(2-amino ethoxymethyl)-4-(2-chlorophenyl) 1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate benzenesulfonate, $C_{20}H_{25}ClN_2O_5C_6H_6O_3S$. The molecular weight of the base is 409 and the structure is



Amlodipine



Amlodipine besylate

Amlodipine besylate is a white crystalline substance slightly soluble in water (0.2% w/v at 24 °C) and sparingly soluble in ethanol.

The tablets to be marketed are formulated as white, round, normal convex, scored tablets containing 5 mg or 10 mg amlodipine for oral administration. All strengths (2.5, 5, 10mg) were made from a common direct compression blend.

The recommended dose is initially 5 mg once daily with a maximum of 10 mg. Steady state blood levels are reached after 7-8 days.

The amlodipine besylate tablets are intended to be manufactured at two sites, namely:

a) New York, USA
b) Barceloneta, Puerto Rico

In a telephone conversation with Dr.Hockel of Pfizer and Dr.Parekh of the Division of Biopharmaceutics, FDA, on June 8, 1988, the Sponsor informed that Pfizer originally intended to market the maleate salt of amlodipine. As a result, clinical studies were conducted with amlodipine maleate tablets and capsules (the capsules were used by the European counterparts). The maleate salt however, had formulation (tableting) and stability problems. The firm therefore switched to the besylate salt of amlodipine. In the submission dated 2/22/90, the firm stated that the maleate and besylate formulations used in the biopharm studies were also used in pivotal clinical studies. A list of formulations used in the clinical and bio studies is attached. It is not very clear as to what formulations were clinically tested. (The Medical Reviewer should be made aware of this stability problem of the maleate salt and its implications in safety and efficacy trials).

Studies Reviewed:

1. Open two-way cross-over study in normal male volunteers to study the pharmacokinetics of amlodipine maleate administered orally as capsules and by intravenous infusion. (Vol. 1.17, Study #208)

2. Open three-way cross-over study in healthy male volunteers, to study the pharmacokinetic properties of amlodipine maleate administered as solution and capsules and amlodipine benzene sulfonate administered as tablets. (Vol. 1.18, Study #214)

3. Open two-way cross-over study in healthy male volunteers to study the pharmacokinetic properties of amlodipine administered orally as the maleate salt in solution and as the benzene sulfonate salt in capsule formulations. (Vol. 1.18, Study #215)

4. Open two-way cross-over study in normal male volunteers to study the pharmacokinetics of amlodipine administered orally as the maleate salt in solution and in capsules. (Vol. 1.19, Study #203)

5. Double blind, placebo controlled, fourteen day evaluation of amlodipine 15 mg/day, administered to normal volunteers. (Vol. 1.19, Study # 209)

6. To study the pharmacokinetics of a range of oral doses of amlodipine in normal volunteers. (Vol. 1.17, Study #201)

7. An open dose-ranging evaluation of single intravenous doses of amlodipine administered to normal male volunteers. (Vol. 1.17, Study #205)

8. Pharmacokinetics of amlodipine in healthy volunteers: A three-way crossover comparison of 2.5, 5 and 10 mg single oral doses. (Vol. 1.22, Study #006)

9. Double blind, placebo controlled, sequential parallel group study of 7 days treatment at 3 dose levels of amlodipine capsules. (Vol. 1.21, Study #202)

10. An open study in normal male volunteers of the absorption, metabolism and excretion of radiolabeled amlodipine maleate given orally and intravenously. (Vol. 1.27, Study 206/207)

11. An open two-way crossover study in normal male volunteers to examine the effects of food on the pharmacokinetics of a single oral dose of amlodipine. (Vol. 1.23, Study #210)

12. An open study in elderly volunteers to examine the pharmacokinetics of a single dose of amlodipine administered orally by capsule. (Vol. 1.25, Study # 211/211A)

13. An open study to compare the pharmacokinetics of oral amlodipine in patients with renal insufficiency and in healthy subjects. (Vol.1.24-1.25, Study # 368)

14. To determine the pharmacokinetic profile of amlodipine after a single oral dose in patients with mild hypertension at dose levels ranging from 0.5 to 20mg. (Vol.1.16, Study # 001)

15. The pharmacokinetic interaction of amlodipine and digoxin in healthy volunteers. (Vol.1.23-1.24, Study # 005)

16. A two-way crossover study to evaluate the pharmacokinetics of a single oral dose of amlodipine when co-administered with single blind cimetidine or placebo to healthy volunteer subjects. (Vol.1.24, Study # 216)

17. Protein binding of (^{14}C]amlodipine in the plasma of rat, dog and man. (Vol.1.28)

18. Investigations on the protein binding of digoxin, indomethacin, phenytoin and warfarin to human plasma in the presence of amlodipine. (Vol.1.28)

19. In-vitro dissolution for amlodipine besylate tablets. (Vol.1.16)

20. Proportions of amlodipine enantiomers in human plasma. (Vol.1.28)

21. Review of the package insert. (Vol.1.1)

SUMMARY REPORT

General Pharmacokinetics in Humans: Amlodipine maleate administered as solution and capsule and amlodipine besylate administered as tablet and capsule were found to bioequivalent. Oral administration results in a slow absorption with a Tmax of about 6-13 hours, with a slow elimination half life of about 21-50 hours. The Tmax were similar between tablets, capsules and solutions. Intravenous administration of amlodipine results in a biphasic decline (Study 208, 205, 206/207) with a rapid distribution for about 4-6 hours, t1/2 of 0.1-0.26 hours, followed by slow elimination with a half-life of about 26-44 hours. The volume of distribution is high, about 1400 liters. The total plasma clearance was 546 ml/min. The pharmacokinetic parameters from different studies are summarized:

Study#	total oral dose, mg	N	Cmax ng/ml	AUC ng.hr/ml		t1/2 hours	Tmax hours	SD/MD
208	10 (mc)	12	5.86(1.18)	238(53)	0-inf	33.8	7.6(1.8)	SD
214	20 (mc)	17	11.55(3.1)	585(238)	0-inf	40.7(7.8)	9.4(2.9)	SD
	20 (bt)	17	11.64(3.3)	598(236)	0-inf	42.1(7.9)	9.2(1.9)	SD
	20 (ms)	17	11.62(3.5)	590(225)	0-inf	41.6	10(2.4)	SD
215	20 (bc)	12	8.76(2.74)	385(144)	0-192	43.6	7.3(1.6)	SD
	20 (ms)	12	8.36(2.42)	362(144)	0-192	43.9	7.3(1.8)	SD
203	20 (mc)	12	10.4(1.05)	464(100)	0-inf	37.8(7.1)	7.2(1)	SD
	20 (ms)	12	9.64(1.55)	456(116)	0-inf	37(7.6)	8.2(2)	SD
209	15(mc) day 1	28	6.93(2.6)		0-inf		8.9(3.7)	MD
	day 14	28	18.07(7.1)	348(139)	0-24	44.7(8.6)	8.7(1.9)	
201	10 (mc)	2	12.3, 7.6	390, 281	0-48		8, 8	SD
	15 (mc)	2	10.6, 9.4	245, 234	0-48	31, 21	6, 13	SD
	20 (mc)	2	10.5, 7.1	305, 157	0-48	29,	6, 13	SD
006	2.5 (bt)	12	1.26(0.26)	41(12.2)	0-72	31.2	5.4(1.7)	SD
	5.0 (bt)	12	2.66(0.54)	94.3(22)	0-72	33	6.3(3.1)	SD
	10 (bt)	12	5.49(1.31)	200(45)	0-72	36.8	6.4(2.7)	SD
	2.5 (bt)			54.3(19.7)	0-inf			
	5.0 (bt)			124(33.94)	0-inf			
	10 (bt)			279.5(82.6)	0-inf			
002	10(mc) day 1	6	4.7(1.1)	71(23)	0-24		7.7(2.7)	MD
	day 14	6	11(5.8)	217(119)	0-24	53.3	6(1.8)	
	15(mc) day 1	9	8(2.4)	121(36)	0-24		8(2.5)	MD
	day 14	9	6.9(2.5)	494(171)	0-24	53.3	6.9(2.5)	
202	2.5(mc) day 1	4	1.7(1.1)	21(9.3)	0-24		7.5(1)	MD
	day 7	4	3.3(1.3)	54.3(25)	0-24	27.5	8(2.8)	
	5.0(mc) day 1	4	3.6(1)	48.5(10.9)	0-24		8(2.8)	MD
	day 7	4	9.9(4.6)	169.6(94.8)	0-24	34.7	8.5(2.5)	
	7.5(mc) day 1	4	3.3(1)	50.2(20.3)	0-24		7(1.1)	MD
	day 7	4	11(5.9)	176(78)	0-24	35.5	8.5(2.5)	
206/207	15(C14)	2	6.7, 5.6	218, 261	0-inf	36, 30	8, 12	SD
210	10(mc) fast	12	4.26(1.24)	168(67)	0-144	41.3	8(2.4)	SD
	fed	12	4.38(1.16)	178(64)	0-144	39.8	8(1.9)	SD

m=maleate, b=besylate, c=capsule, t=tablet, s=solution, SD=single dose, MD=multiple dose, C14=radiolabel

Absorption, Distribution, Metabolism, Excretion: After single IV (5mg) and oral (15mg) doses of ^{14}C-amlodipine to 2 volunteers, absolute bioavailability of 60-65% was reported, indicating about 30% first pass. The total radioactivity in plasma was about 10 fold the unchanged drug and had nearly twice the terminal half-life. About 61% of the administered radioactivity was recovered in urine while fecal elimination accounted for about 20-25% of the radioactive dose. Similar % of the radioactive dose were recovered in the urine and feces after oral or IV administrations, indicating complete oral absorption. This, along with the patterns of plasma concentrations, indicate possibility of recirculation. Total recovery over 14 days in urine and feces was 76-90% of the dose. Nine (9) major metabolites were identified which, being the pyridine metabolites, are devoid of calcium antagonistic activity (it is recommended that this study be reviewed by the pharmacologist).

The plasma protein binding was studied at the concentrations 50 and 500 ng/ml, using equilibrium dialysis with pH 7.4 buffer at 37°C. Both concentrations are above the expected therapeutic concentrations. At these concentrations, amlodipine was found to be 97.5% and 96.2% resp. bound (in-vitro). In-vitro protein binding of digoxin, indomethacin, phenytoin and warfarin were studied in presence of amlodipine. A mean of 5 determinations showed that indomethacin, phenytoin and warfarin binding did not change in presence of amlodipine. Digoxin protein binding was 46(±3.3)% and in presence of amlodipine was 40.9(±3.4)%. If this change in the binding were significant, it did not influence the pharmacokinetics of either amlodipine or digoxin, as shown in the Study 005. (The assay validation for the RIA for digoxin was not submitted so the conclusion for digoxin is provisional).

Amlodipine is a racemic mixture of the R(-) (active isomer) and the S(+) isomers. The proportions of the enantiomers remained constant in the systemic circulation for upto 24 hours after a single oral dose of 20mg. The last sampling time was 48 hours, at which time the R:S ratio increased slightly (by about 7.5% and 11% in the 2 subjects studied). Since the drug half life is about 20-50 hours, this is only partial information on the relative pharmacokinetics of the individual isomers.

Dose Proportionality: Information from several studies was used in order to identify the dose proportionality (in the recommended dose range). Accumulation ratio of 2.6-3.6 (Study 209, 15mg/day for 14 days) is in accord with the theoretical prediction for linear drug with τ=24 hours and t1/2 of 45 hours. In Study 201, administration of 10, 15 and 20mg po to 2 subjects each, showed large variability between subjects. Although no dose related trend was seen, the study was inconclusive with regard to the dose proportionality due to the variability in the data. In Study 205, 1.25-15mg of amlodipine was administered IV in pairs. The plasma concentration profiles were biphasic with indications of recirculation. The pharmacokinetics were apparently linear based on the AUC(0-inf) for all subjects. In Study 006, 2.5mg, 5mg and 10mg were administered po as single doses crossed-over in 12 subjects. Dose proportionality could be concluded based on the 5mg and 10mg administrations, which are the recommended therapeutic doses. The dose normalized AUC from the 2.5mg dose were lower however, this may be attributed to low plasma concentrations in the region of the assay detection limit. Study # 202

was a parallel multiple dose, dose ranging study with 4 subjects in each dose group of 2.5, 5 and 7.5 mg q.d. for 7 days. The Cmax and AUC were proportionate to the dose. Study # 001 was in mildly hypertensive patients where 0.5-20mg were administered as incremental doses with 3-4 subjects at each dose. A linear increase in the AUC and Cmax with dose was observed, however, one of the three subjects studied at the 20mg dose showed a disproportionately high Cmax and AUC. The highest dose recommended however, is 10mg/day.

Food Effect on Pharmacokinetics: This was studied in 12 subjects and the "fed" state breakfast consisted of milk, bread and butter, bacon and decaffeinated coffee. Food did not effect the pharmacokinetics of amlodipine.

Special Populations: Pharmacokinetics of amlodipine were investigated in 'healthy' elderly males and females (Study 211/211A), in patients with different degrees of renal dysfunction (Study 368) and in patients with mild hypertension (Study 001).

Study#	Population	N	Dose,mg	Cmax	AUC	Tmax	t1/2
211/211A	elderly						
	male	8	5 (mc)	2.46(0.3)	161(55) 0-inf	7(1.9)	46.9
	female	8	5 (mc)	4.1(1.37)	240.5(105) "	8.3(2.7)	41.3
368	renal failure GFR (ml/min)						
	38-65	6	5(mc) day 1	3.6(1.2)	58(19) 0-24	6(1.3)	
			day 14	10.9(2.8)	210(42) 0-24	5(1.1)	52.1
	20-29	5	5(mc) day 1	3.5(1.4)	61(23) 0-24	8.4(3.3)	
			day 14	11.4(4.7)	262(63) 0-24	6.4(1.7)	46.2
	7-15	6	5(mc) day 1	2.4(0.6)	39(11) 0-24	5.7(2)	
			day 14	6.2(3.2)	127(67) 0-24	5.3(1.6)	41.7
	0-2	4	5(mc) day 1	2.3(0.3)	35(7) 0-24	5(2.6)	
			day 14	7.8(2.5)	147(59) 0-24	6(1.6)	50.6
	104-126 (normal)	6	5(mc) day 1	2.5(1)	44(16) 0-24	9.3(3.3)	
			day 14	6.3(1.7)	118(36) 0-24	7(3)	37.7
001	mild hypertension						
		3	1(mc)	0.8(0.2)		10.7(2.3)	
		4	2.5(mc)	1.6(0.8)		7(1.2)	
		4	5(mc)	2.2(0.3)	85(10) 0-72	8.5(2.5)	
		4	10(mc)	5.1(1.4)	171(42) 0-72	8.5(2.5)	38.5
		4	15(mc)	5.5(1.5)	256(90) 0-72	8.5(3.0)	63
		3	20(mc)	13.4(5.9)	428(232) 0-72	6.7(1.2)	49.5

Elderly females showed nearly twice the Cmax and AUC of the elderly and young healthy males. The pharmacokinetics study in renally impaired patients showed that subjects with GFR ranging from 20-65 ml/min had higher Cmax and AUC than the normals on day 14. Patients with GFR ranging from 0-15 showed no Cmax and AUC differences from those of the normals. Hypertension did not influence the pharmacokinetics of amlodipine.

Drug Interactions: Coadministration with either digoxin (Study 005) or cimetidine (Study 216) did not influence the pharmacokinetics of amlodipine.

Assay procedure: A gas chromatograph fitted with a capillary column and an electron capture detector were used for analyzing human plasma. The method involved injection of the trimethylacetyl derivative of amlodipine and the internal standard (UK-52,829). The accuracy and reproducibility were evaluated with each study. Generally, with each biopharmaceutics study, the plasma samples were analyzed in batches comprising of all samples from one subject with daily calibration standards, and approximately 10% of the total number of test samples as quality control standards. Approximately 10% repeat analyses were also performed.

Overall Comments:

1. Pfizer originally intended to market the maleate salt of amlodipine. I was informed that the the maleate salt had tableting and stability problems and the final marketed product was thus the besylate salt of amlodipine. Upon enquiring with the firm, I was informed (Supplement dated 2/22/90) that the maleate and besylate salts used for the biopharm studies were also used in pivotal clinical studies; this however is not very obvious from the submitted list of products used in these studies. The Chemist and the Medical Reviewer should be informed of this; its implications in terms of the clinical safety and efficacy studies should be evaluated by the Clinician; please refer to the ATTACHMENT at the end of the review.

2. Upon administration of C14-amlodipine, total radioactivity was 10 times higher than the radioactivity allocated to the parent drug. The half life for total radioactivity was also higher, about 100 hours. Nine major metabolites were identified. The firm has stated that these are the pyridine metabolites and therefore devoid of Ca-antagonistic activity. The pharmacologist is requested to review the Study # 206/207, Vol. 1.27 which supports this claim.

3. A study in normotensive elderly subjects conducted over two periods of time separated by about 1 year showed that the Cmax and AUC parameters for elderly females were about 2 times those of the elderly and young healthy males. This observation is made based on the study using 8 subjects each of elderly males and females and cross study comparison with young healthy male subjects. This information should be forwarded to the medical officer.

4. Patients with mild hypertension were studied at doses ranging from 0.5 to 20 mg single doses. The results represent combined data from 2 centers. About 3 or 4 patients were studied at each dose. The clinician should be informed that although dose proportionate AUC and Cmax were observed upto the 15mg dose, one of the three subjects studied at 20mg dose showed a disproportionately high AUC and Cmax. (Also note that the 20mg dose is higher than the daily recommended dose).

5. Although metabolism is a major pathway of elimination, hepatic patients have not been investigated.

6. The in-vitro protein binding was studied at 50 and 500ng/ml concentrations. These are higher than the therapeutic concentrations observed in the submitted studies. Protein binding should be studied at concentrations in the therapeutic range.

7. In-vitro dissolution should be characterized in various pH media. Based on the current dissolution data, the specification proposed is too liberal since almost 100% of the drug dissolved by 30 minutes. A specification of NLT 85% at 30 minutes would be more appropriate.

8. The following comments pertain to labeling; a copy of the package insert is attached in the Appendix:

a. Based on the information submitted in the studies, 0-72 hour urine sample was assayed for differential analysis to show that 35-45% of dose was recovered in the urine during this time period. (Total urinary recovery was about 60% of the administered dose). Of the total radioactivity recovered in urine over 0-72 hours, about 10% was attributed to the parent drug. The labeling states that amlodipine is extensively (about 90%) converted to inactive metabolites, with 10% of the parent drug and 60% of the metabolites excreted in the urine. This statement is incorrect. Actually there is insufficient data to state the % of dose excreted unchanged in the urine. Since the drug has a half-life of about 40 hours, 72 hours urinary recovery is insufficient to make any definite labeling statements. The firm should either submit additional data with complete urinary recovery information on parent drug and metabolites or report the actual results from the 0-72 hours urinary data or totally exclude such specific statements from the package insert.

b. Since the hepatic patients have not been investigated, this should be mentioned in the 'Pharmacokinetics and Metabolism' and the 'Precautions' sections.

c. Some differences were apparent between the categories of renal patients and healthy subjects however no pattern was observed to correlate degree of renal dysfunction and pharmacokinetics of amlodipine. Comparison of the pooled renal patients data with normals showed no significant differences in Cmax and AUC. Categories 1 and 2 (GFR 20-60 ml/min) however, had significantly higher Cmax and AUC values on day 14, as compared to normal subjects. No difference was detected on day 1. Although Categories 3 and 4 had more severe renal impairment (GFR 0-15 ml/min), no differences in Cmax and AUC were detected as compared to the normals. The firm's labeling states '..since blood levels of amlodipine do not correlate with the degree of renal failure, upwards titration should be carried out slowly and carefully.' The clinician (HFD-110) is requested to further evaluate this and suggest the necessary changes in the labeling.

d. Regarding the plasma protein binding, labeling should state that amlodipine is 97.5% and 96.2% bound at concentrations of 50 and 500ng/ml respectively. The 'Drug Interactions' section states that amlodipine has no affect on protein binding of drugs tested (digoxin, phenytoin, warfarin or indomethacin)'. Digoxin protein binding however, decreased by about 11% in presence of amlodipine. Labeling should be corrected to relate this.

e. The labeling states '...although elderly patients may have higher plasma concentrations of amlodipine than those in younger patients....' which is incorrect based on the Study # 211/211A. This study with 8 elderly males and females showed that elderly females have nearly twice the Cmax and AUC values as the elderly and young healthy males. The Clinical Division is requested to review this section and its relevance to labeling. In reference to the elderly, labeling also states 'Treatment with Amlodipine is well tolerated in the elderly and therefore, normal dosage regimens are recommended.'

f. The label states 'Elimination from plasma is biphasic with a terminal elimination half-life of about 35-50 hours.' The firm should state 'Intravenous administration of amlodipine showed that the elimination from plasma is biphasic with a terminal elimination half-life of about 35-50 hours.'

g. The label states '...amlodipine may be used safely in combination with a thiazide diuretic, a beta adrenoceptor blocking agent or an angiotensin converting enzyme inhibitor...', and '...amlodipine may be used in combination with other antianginal drugs such as nitrates or beta blockers...'; biopharmaceutics studies have been submitted only with digoxin and cimetidine. HFD-110 is requested to check on the validity of the above statements in the package insert.

Recommendation:

The Division of Biopharmaceutics has reviewed Vol.1.16-1.28 of NDA 19-787 dated 12/22/87, 8/2/88 and 2/22/90 for amlodipine tablets and finds the Pharmacokinetics/Biopharmaceutics section acceptable. Comments 1-3 and 8 c, e and g under Labeling should be evaluated by the Clinician. The firm should incorporate the labeling changes recommended in Comments 8 a-g, and respond to Comments 6 and 7 regarding protein binding and in-vitro dissolution.

The firm should send samples (3 x 100 dosage units) of the commercial lots evaluated in the pivotal BA/BE studies for our lab use. Samples for additional proposed strengths not included in the BA/BE studies should also be submitted. The firm should provide the lot number(s), lot size(s), strength(s), date(s) of manufacture and expiration dates for the samples submitted. For the lots used in the BA/BE studies, the study numbers should be identified. These samples along with the above information should be sent to:

Dr. Gerald Shiu
Biopharmaceutics Research Laboratory
Federal Office Building 8
Room 2884
HFD-424
200 C Street, SW
Washington, DC 20204

Ameeta Parekh 10/1/90
Ameeta Parekh, Ph.D.
Pharmacokinetics Evaluation Branch

cc: NDA 18-787 Orig., HFD-110, HFD-426 (Parekh), HFD-344 (Turner), Drug and Chron files

ANP:arp:PC:8/4/88, 8/1/90, 9/4/90, 10/1/90